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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/770,602	01/26/2001	Sudhir Agrawal	47508.701	6891

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EXAMINER

ZARA, JANE J

ART UNIT

PAPER NUMBER


1635

DATE MAILED: 01/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

A. File

Office Action Summary

Application No. 09/770,602	Applicant(s) Agrawal	
Examiner Jane Zara	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Nov 6, 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-60 is/are pending in the application.
- 4a) Of the above, claim(s) 1-15 and 24-60 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 16-23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 3 6) ☐ Other:

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DETAILED ACTION

This Office action is in response to the communication filed November 6, 2002, Paper No.

6.

Election/Restriction

Applicant's election without traverse of Group II in Paper No. 6 is acknowledged.

Claims 1-15, 24-60 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 6.

Specification

The specification is objected to because on page 31, in Example 2, a mouse spleen cell proliferation assay referred to Example 1 for the protocol description, but Example 1 lacks such a description. Appropriate clarification is requested.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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In claims 16, 18 and 22, lines 7-11, the term “4th nucleoside 3' to the CpG dinucleotide” is repeated several times. Appropriate clarification is requested.

The metes and bounds of the term “increasing the immunostimulatory effect” in claim 16, line 1, and of the term “having increased stimulatory effects” in claim 18, lines 1-2, are vague and unclear. Appropriate clarification is requested.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing mouse spleen cell proliferation in vitro and in vivo comprising the administration of 3'-O-methyl ribonucleoside, 2'-5' methyl phosphonate internucleotide-containing CpG oligonucleotides, whereby the 3'-O-methyl ribonucleosides are located 3 or 4 nucleosides 5' to the CpG dinucleotide, does not reasonably provide enablement for compositions and methods for increasing immunostimulatory effects in vitro and in vivo in any and/or all organisms comprising the administration of 3'-substituted CpG-containing oligonucleotides, whereby the 3'-substitutions occur between 3-6 nucleosides 5' from the CpG dinucleotide, or 2-6 nucleosides 3' of the CpG dinucleotide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

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The claims are drawn to methods and compositions for increasing immunostimulatory effects in vitro and in vivo in any organism comprising the administration (by any route) of 3'-substituted CpG-containing oligonucleotides, whereby the 3'-substitutions occur between 3-6 nucleosides 5' from the CpG dinucleotide, or 2-6 nucleosides 3' of the CpG dinucleotide.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. CpG containing oligonucleotides are currently being investigated for exerting their immunotherapeutic effects in various organisms (See Krieg et al, Weiner and McCluskie et al for recent advances using CpG oligonucleotides). Biological responses to the administration of CpG containing oligonucleotides vary, however, depending on the mode of administration and the organism (See McCluskie et al in its entirety, and especially on page 296; Also see Krieg et al on page 524). Weiner states furthermore that the molecular mechanisms of CpG oligonucleotides' immunostimulatory effects are not yet understood (See especially page 461). And while the biological effects of some chemical modifications have been studied for CpG containing oligonucleotides, such as 2'-O-methyl modifications, phosphorothioate internucleotide linkages and 5-methyl cytosine substitutions, the incorporation and positioning of chemical modifications relative to the CpG dinucleotide are highly unpredictable (See Agrawal et al especially on pages 78-80; See also pages 31-32 of the instant specification).

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The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of increasing immunostimulatory effects comprising the administration of any oligonucleotide comprising 3'-substituted CpG-containing oligonucleotides, whereby the 3'-substitutions occur between 3-6 nucleosides 5' from the CpG dinucleotide, or 2-6 nucleosides 3' of the CpG dinucleotide. The specification teaches an increase in mouse spleen cell proliferation in vitro and in vivo comprising the administration of 3'-O-methyl ribonucleoside, 2'-5' methyl phosphonate internucleotide-containing CpG oligonucleotides, whereby the 3'-O-methyl ribonucleosides are located 3 or 4 nucleosides 5' to the CpG dinucleotide. One skilled in the art would not accept on its face the examples given in the specification of increasing spleen cell proliferation in vitro and splenomegaly in vivo comprising the administration of 3'-O-methyl ribonucleoside, 2'-5' methyl phosphonate internucleotide-containing CpG oligonucleotides, whereby the 3'-O-methyl ribonucleosides are located 3 or 4 nucleosides 5' to the CpG dinucleotide, as being correlative or representative of the successful immunostimulation in any organism comprising the administration by any route of any oligonucleotide comprising 3'-substituted CpG-containing oligonucleotides, whereby the 3'-substitutions occur between 3-6 nucleosides 5' from the CpG dinucleotide, or 2-6 nucleosides 3' of the CpG dinucleotide in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the biological effects exerted by CpG containing oligonucleotides in any and/or all organisms and further comprising any 3'-substitutions relative to the CpG dinucleotide. The

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specification as filed fails to provide particular guidance which resolves the known unpredictability in the art associated with effects provided in vivo in any and/or all organisms upon administration via any route of CpG containing oligonucleotides, and specifically regarding the incorporation of 3'-modifications into such oligonucleotides in any and/or all organisms.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to methods and compositions for increasing immunostimulatory effects in vitro and in vivo in any organism comprising the administration by any and/or all routes of 3'-substituted CpG-containing oligonucleotides, whereby the 3'-substitutions occur between 3-6 nucleosides 5' from the CpG dinucleotide, or 2-6 nucleosides 3' of the CpG dinucleotide. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues in any and/or all organisms, and further whereby immunostimulatory effects are provided. Since the specification fails to provide particular guidance for biological effects exerted by CpG containing oligonucleotides in any and/or all organisms and further comprising any of the 3'-substitutions listed relative to the CpG dinucleotide, and since determination of these factors for a particular modification, position relative to the CpG dinucleotide, route of administration and organism is highly unpredictable, it would require undue experimentation to practice the invention over the broad scope claimed.

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Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 18, 20 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Baracchini et al.

Baracchini et al teach CpG containing oligonucleotides having increased immunostimulatory effects, whereby 3'-substitutions occur between 3-6 nucleosides 5' from the CpG dinucleotide, or 2-6 nucleosides 3' of the CpG dinucleotide, and which oligonucleotides are between 6-50 nucleobases in length and comprise modified internucleotide linkages (See especially Baracchini et al at col. 6-7).

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Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is (703) 306-5820. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ

January 7, 2003


KAREN LACOURCIERE
PATENT EXAMINER